SOT 2017 Symposium Proposal

PRESENTATION TYPE: Symposium
Requested Sponsors:

Title: PCB exposure and non-cancer outcomes: consideration of toxicological and mechanistic evidence

Abstract:
Polychlorinated biphenyls are persistent organic pollutants characterized by a chlorine-substituted biphenyl structure, resulting in 209 possible congeners. In the environment, PCBs occur as mixtures of congeners, and exposure is associated with cancer and non-cancer health outcomes. Depending on their congener composition, PCB mixtures can disrupt specific biological networks, leading to toxicological effects. Consideration of the pathways and mechanisms associated with specific health outcomes is an important component of hazard evaluation. The United States Environmental Protection Agency (U.S. EPA) National Center for Environmental Assessment (NCEA) is currently developing a new PCB assessment that considers non-cancer effects. This session will highlight the current state of research concerning PCBs and mechanisms associated with various non-cancer health outcomes. Platform presentations will focus on the impact of PCB exposure on cardiovascular, hepatic, developmental and neurological effects observed in in-vivo and in-vitro studies, and approaches used for hazard evaluation and integration of mechanistic and toxicological evidence.

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Title of Workshop: PCB exposure and non-cancer outcomes: incorporation of mechanisms specific to co-planar and non-coplanar congeners

Introduction:

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Presentation #1: PCBs and cardiovascular effects: cellular/molecular, and in-vivo responses.

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Synopsis: Cardiovascular disease (CVD) is the leading cause of death in the United States for both men and women and is associated with multiple modifiable and non-modifiable risk factors. CVD however is not a singular pathology but a group of disorders encompassing the heart, blood vessels, and associated tissues. Epidemiological studies have now linked exposures to polychlorinated biphenyls (PCBs) with an increased risk of developing CVD and CVD-related pathologies including alterations of blood pressure and lipid profiles, obesity, and diabetes. Mechanistic cellular and molecular studies have identified multiple pathways, such as the aryl hydrocarbon receptor (AhR) and NFκB pathways that are critical to PCB-induced vascular diseases. Using well characterized animal models of CVD, PCBs have been shown to promote or exaggerate multiple risk factors related to atherosclerosis. Emerging data now suggests that PCB-induced CVD may be ameliorated or exacerbated by secondary stressors such as diet. As more is learned about the interactive effects of PCBs and other stressors, additional future human studies are critical to identify sensitive and highly susceptible populations which may be more prone to PCB-induced CVD and related diseases.

Presentation #2 (tentative title): PCBs and hepatic effects.

Speaker Information:

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Synopsis: Polychlorinated Biphenyls (PCBs), especially dioxin-like PCBs, exemplified by 3,3',4,4',5-pentachlorobiphenyl (PCB126), a potent aryl hydrocarbon receptor (AhR) agonist, exert a broad range of adverse hepatic changes, including a disruption of both carbohydrate and lipid metabolism which ultimately leads to wasting disorders, metabolic disease, and non-alcoholic fatty liver disease (NAFLD), and trace element homeostasis. Liver, responsible for metabolic homeostasis, is a target organ for PCB toxicity. In a time course of events following PCB126 administration, we observed an early decrease in

serum glucose and a gradual decrease in serum triglycerides over time. Liver lipid accumulation was most severe at later times of exposure. The changes observed in the hepatic architecture, i.e. accumulation of lipid in vacuoles, appears to also disrupt the trace element/micronutrient homeostasis as most severe changes that occur at later time points. Additionally investigations suggest that disruptions of intra-acinar micronutrient gradients leads to the overt micronutrient dyshomeostasis. The implications of alterations in gradients across the acinus could also affect other homeostatic functions of the liver including glucose and lipid metabolic pathways, such as gluconeogenesis and fatty acid oxidation. In particular, the transcript and protein levels of cytosolic phosphoenol-pyruvate carboxykinase and a glucose transporter involved in gluconeogenesis and hepatic glucose transport, were time-dependently downregulated.

Presentation #3 (tentative title): Cellular and molecular mechanisms of PCB developmental neurotoxicity.

Speaker Information:

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Synopsis: This presentation will summarize both *in vivo* and *in vitro* studies demonstrating that non-dioxin-like (NDL) PCBs modulate Ca^{2+}-dependent signaling pathways that regulate neuronal connectivity. Specifically, data will be discussed that support an adverse outcome pathway in which the molecular initiating event is sensitization of ryanodine receptors in neurons that activates Ca^{2+}-dependent signaling pathways that control activity-dependent dendritic arborization and excitatory synapse formation as well as neuronal apoptosis, and ultimately causes behavioral deficits in animal models of developmental PCB exposure. The implications of these studies for understanding gene x environment interactions that influence risk and/or severity of neurodevelopmental disorders will also be discussed.

Presentation #4 (tentative title): Maternal PCB Exposure Impacts Physiological Outcomes in Offspring

Speaker Information:

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Synopsis: Obesity and diabetes are at epidemic levels, and the toxicity of environmental contaminants during perinatal development could be a significant contributor to these trends. The goal of our current research is to elucidate the potential long-term health complications and mechanisms of polychlorinated biphenyl (PCB) toxicity during the critical periods of in utero and early postnatal life. In our studies in a mouse model, we are using doses of PCBs that are relevant to human exposures. We have found that PCB126 exposed mouse fetuses have increased markers of oxidative stress and inflammation. We have also found that female offspring born to PCB-exposed dams have impaired glucose tolerance compared to those offspring born to vehicle exposed dams. We are in the process of determining when the critical window of exposure is for the perinatal negative programming associated with PCB126 exposure. Further, we will assess measures in both male and female offspring to determine if both sexes are affected equally.

Presentation #5 (tentative title): PCBs and Human Health Risk Assessment: Considerations for Integrating Experimental and Mechanistic Evidence for Noncancer Health Effects.

Speaker Information:

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Synopsis: Although the commercial manufacture of PCBs has been banned in many countries for several decades, PCBs are still found in the environment, and human exposure to these chemicals continues. Currently, noncancer human health risk associated with PCB exposure is often assessed using Integrated Risk Information System (IRIS) reference doses (RfDs) available for the commercial PCB mixtures Aroclor 1016 and Aroclor 1254. These RfDs were developed using toxicological data available in the early 1990s. However, PCB research since that time has provided new information to consider, including mechanistic data that may be useful for understanding associations between PCB exposure and a wide range of health effects. In this presentation, putative modes of action will be discussed for some of the noncancer health outcomes more commonly associated with PCB exposure, with an emphasis on the utility of this information for hazard evaluation.